THE FIRST GENERATION OF ORALLY-ACTIVE NPY Y_1 RECEPTOR ANTAGONISTS: PHARMACOLOGICAL PROFILE OF SR 120819A, C. Serradeil-Le Gal, Sanofi Recherche, 195 route d'Espagne, 31036 Toulouse Cedex, France

Since NPY and related peptides, PYY and PP, exert their multiple effects through at least six receptor subtypes (Y_1, Y_2, Y_3, PP_1/Y_4, PYY-preferring and "appetite" receptors), there is a crucial need for specific tools to identify each entity and its functions. The last few years have shown significant progress in this field thanks to the cloning of receptors of the NPY family (Y_1, Y_2 and PP_1/Y_4) and to the design of the first potent and selective Y_1 receptor antagonists. We report here the discovery of the first generation of orally-active NPY Y_1 receptor antagonists, illustrated by SR 120819A. SR 120819A (1-[2-[2-(2-naphtylsulfamoyl)-3-phenylpropionamido]-3-[4-[N-[4-(dimethylaminomethyl)-cis-cyclohexylmethyl]amidino]propionyl]-pyrrolidine) displays highly selective and competitive affinity for NPY Y_1 receptors from various species including man (K_i = 15 nM). Specific functional antagonism at Y_1 receptors has been demonstrated *in vitro* and *in vivo*, without observing any agonistic effects whatever the preparation used. Investigated in two Y_1 *in vitro* models, SR 120819A dose-dependently antagonized the inhibitory effect of NPY on adenylyl cyclase activity in the human neuroblastoma SK-N-MC cell line and counteracted the inhibitory effect of the Y_1 agonist, [Leu^{31},Pro^{34}]-NPY, in the rabbit *vas deferens* (pA_2 = 7.20 ± 0.07). *In vivo*, intravenous SR 120819A competitively blocked NPY-induced arterial blood pressure increase in pithed rats. Remarkably, both by intravenous (0.1 - 1 mg/kg) and by oral (1 - 10 mg/kg) routes, SR 120819A antagonized the [Leu^{31}, Pro^{34}]-NPY-induced hypertension in anaesthetized guinea-pigs with a long duration of action (> 4 H at 5 mg/kg p.o.). In addition, we demonstrated that SR 120819A constitutes a major tool for the characterization and localization of Y_1 receptors and potential subtypes in complex organs such as the rabbit kidney expressing mixed populations of NPY receptor sites. Thus, SR 120819A is the first powerful, selective, orally-effective NPY Y_1 antagonist yet described. This molecule represents the prototype of the first generation of *in vivo* active NPY Y_1 antagonists and is of relevance for understanding the pathophysiological role of NPY, Y_1 receptor functions and for developing compounds for therapeutic applications.